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Attachment (Page 9)



Marked Up Version of Amended Paragraphs

Paragraph replaced on Pages 13-14

According to the practice of the invention, a protein of the p53 family is defined as a mammalian p53, p63, or p73; and/or a protein that possesses a domain, all having at least 50%, more preferably 80%, of amino acid sequence homology to one or more of (1) the N-terminal domain required for transcriptional activation, (2) the DNA-binding domain, or (3) the oligomerization domain of a mammalian p53, p63, or p73, wherein said homology is measured by any of the recognized algorithms BLASTP v. 2.0 [(www.ncbi.nlm.nih.gov)] (Alschul et al., 1990, J. of Molec. Biol., 215:403-410, "The BLAST Algorithm; Altschul et al., 1997, Nuc. Acids Res. 25:3389-3402) and W.U.-BLAST-2.0 (available from Washington University, St. Louis, MO, USA), and wherein said protein evidences at least one function that is recognized in the art as characteristic also of p52, p63, or p73 (e.g. for example, capability of activating p53 responsive promoters and induce apoptosis; for discussion of art-recognized properties, see Kaelin, 1999; Yang et al., 1998; and Yoshikawa et al., 1999, cited above). For general discussion of the procedure and benefits of the BLAST, Smith-Waterman and FASTA algorithms see Nicholas et al., 1998, "A Tutorial on Searching Sequence Database and Sequence Scoring Methods" [(www.psd.edu)] and references cited therein.

Paragraph replaced on Pages 36-37

In other embodiments, binding can be detected without making use of a direct or indirect label. For example, a biophysical property which alters when binding occurs can be assayed. A solid support system particularly advantageous for such screening is the BIAcore 2000TM system, available commercially from BIAcore, Inc. (Piscataway, NJ). The BIAcoreTM instrument [(<http://www.biacore.com>)] uses the optical phenomenon of surface plasmon resonance (SPR) to monitor biospecific interactions in real-time. The SPR effect is essentially an evanescent electrical field that is affected by local changes in refractive index at a metal-liquid interface. A sensor chip made up of a sandwich of gold film between glass and a carboxymethyl dextran matrix to which the ligand or protein to be assayed is chemically linked. This sensor chip is mounted on a fluidics cartridge forming flow cells through which analyte compounds can be injected. Ligand-analyte interactions on the sensor chip are detected as changes in the angle of a beam of polarized light reflected from the chip surface. Binding of any mass to the chip affects SPR in the gold/dextran layer. This change in the electrical field in the gold layer interacts with the reflected light beam and alters the angle of reflection proportional to the amount of mass bound. Reflected light is detected on a diode array and translated to the binding signal expressed as response units (RU). As the response is directly proportional to the mass bound, kinetic and equilibrium constants for protein-protein interactions can be measured.